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1645

Docket No. 1151-4167

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Chang Yi Wang

Serial No.: 09/865,294

Group Art Unit: 1645

Examiner: Sharon Turner, Ph.D.

Filed: May 25, 2001

For: Immunogenic Peptide Composition for the Prevention and Treatment of Altzheimer's Disease

EXPRESS MAIL CERTIFICATE

Express Mail Label No.: **EV 245 492 889**

Date of Deposit: **October 1, 2003**

I hereby certify that the following attached paper(s) and/or fee

1. Amendment and Response under 37 CFR 1.115;
2. Amendment Fee Transmittal;
3. Return postcard

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. §1.10 on the date indicated above and is addressed to the Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450

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Docket No. 1151-4167

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Chang Yi WANG

Group Art Unit: 1647

Serial No.: 09/865294

Examiner: Sharon L. Turner, Ph.D.

Filed: May 25, 2001

For: IMMUNOGENIC PEPTIDE COMPOSITION FOR THE PREVENTION AND TREATMENT OF ALZHEIMER DISEASE

AMENDMENT FEE TRANSMITTAL

Mail Stop Non Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith is an Amendment for the above-identified application.

☒ No additional fee is required.

☐ The additional fee has been calculated as shown below:

CLAIMS AS AMENDED

	Claims Remaining After Amendment	Highest No. Covered by Previous Payments	Extra	Rate	Additional Fee
Total Claims*	48 -	108	0	$18.00/ $9.00	$ 0
Independent Claims	2 -	5	0	$84.00/ $42.00	$ 0
Multiple Dependent Claims	(If claims added by amendment include Multiple Dependent Claim(s) and there was no Multiple Dependent Claim(s) in application before amendment add $280.00 to additional fee ($140.00 for small entity).				$ 0
				TOTAL	$ 0

*Includes all independent and single dependent claims and all claims referred to in multiple dependent claims. See 37 C.F.R. §1.75(c).

☐ Small entity status is or has been claimed.
Reduced Fees Under 37 C.F.R. §1.9(f) paid herewith $_____

☐ _____ Pages Sequence Listing

☐ _____ Computer disk(s) containing substitute Sequence Listing

☐ Statement under 37 C.F.R. §1.825(b) that the computer and paper copies of the substitute Sequence Listing are the same.

☐ A check in the amount of $_____ to cover the filing fee is attached.

☐ Charge fee to Deposit Account No. 13-4500, Order No. _____. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

☒ The Commissioner is hereby authorized to charge any additional fees which may be required for filing this amendment, including all fees pursuant to 37 CFR §1.17 for its timely consideration, or credit any overpayment to Deposit Account No. 13-4500, Order No. 1151-4167. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Dated: October 1, 2003

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IN THE UNTIED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Chang Yi WANG
Serial No.	:	09/865294
Filed	:	May 25, 2001
For:	:	IMMUNOGENIC PEPTIDE COMPOSITION FOR THE PREVENTION AND TREATMENT OF ALZHEIMER DISEASE
Group Art Unit	:	1647
Examiner	:	Sharon L. Turner, Ph.D.
Office Action	:	July 1, 2003

Commissioner of Patents
Washington, D.C. 20231

BOX: NON-FEE Amendment

AMENDMENT AND RESPONSE

PURSUANT TO 37 C.R.F. §1.115

Sir:

This is in response to the office action dated July 1, 2003 for which a response period of three months was set. The present response is timely.

Applicant requests reconsideration of the Office Action dated July 1, 2003 pursuant to the suggestion of Mr. Gary Kunz in a telephone interview on September 25, 2003. The reasons for the request are stated in the Response section.

RESPONSE begin on page 2 of this paper

RESPONSE

Applicant request reconsideration of each and every point raised by the Examiner IN THIS OFF.

Sequence Requirements

The Examiner stated that Applicant has not complied with 37 C.F.R. 1.821-1.825 for sequence listing requirements. She has stated that the non-compliance prevents the examination of the application.

The requirement is not understood. Firstly, the Examiner appears to have examined the application. Secondly, Applicant has submitted a Sequence Listing for the 77 sequences which were presented in the application.

Based on a telephone call to the Examiner, it seems that the Examiner's contention is that the Sequence Listing should also include sequences that are generically claimed. The generic claims in this application are directed to a peptide that may be 20 to 100 amino acids long comprising:

1. a T helper cell epitope, one of SEQ ID NOs:1-64, linked to

2. a B cell epitope that is 10 to 28 amino acids from the N terminal of $A\beta_{1-42}$.

In the application, there is no specific sequence for a generically claimed peptide immunogen. It embraces at a minimum 4480 sequences. It is not understood how Applicant can physically comply with such a requirement.

Applicant understood that Sequence Listing is a tool to help in the examination of the application. Apparently, in the present case, the Examiner is able to proceeded with examination of claims 1-40 despite the rejection. Thus, it appears that the sequence listing that has been provided is adequate and does comply with the rules.

The sequence listing rules as set forth in 37 C.F.R. 1.821 to 1.825 does not state that there must be a sequence listing for generically or sub-generically claimed peptides.

37 C.F.R. 1.821 is directed to all unbranched sequences presented in the application with 4 or more amino acids. The sequences presented are to be listed in a computer readable format. There is nothing in Section 821 that required a listing of sequences that are not in the specification or are generically described without sequences or in generic or sub-generic claims. This rule does not and has not been interpreted to require an Applicant to supply all possible sequences that may be covered by the claimed invention.

37 C.F.R. 1.822 is directed to the symbols and the format to be used for sequence listing.

37 C.F.R. 1.823 is directed to the order in which the information for each sequence in the sequence listing is to be presented.

37 C.F.R. 1.824 is directed to the computer readable format for the sequence listing.

37 C.F.R. 1.825 is directed to the manner in which the amendment of the sequence listing is to be made.

There is nothing in these rules with regard to generic or sub-generic claims comprising a multitude of combined fragments, when each of the fragments are listed in the Sequence Listing.

Since the Examiner seemed to have been able to examine the generic or sub-generic claims, it appears that such a sequence listing is not required and that the rejection of the application for non-compliance of sequence listing rules should be withdrawn as moot.

Applicant wish to point out that Applicant has submitted applications with claims in a similar format and the issue of non-compliance with sequence listing rules for generic claims has never arisen. See, US 6,090,388; US 6,107,021 and US 65,759,551. Apparently, there is some miscomprehension of what is required under the rules.

Restriction/Election of Species Requirement

The Examiner had imposed a restriction requirement between three groups of claims:

1. Claims 1-40 drawn to peptide immunogens and compositions comprising the peptide immunogens, classified in class 530, subclass 300.

2. Claims 41-60 drawn t a method of preventing or treating Alzheimer's disease, classified in class 514, subclass 2.

3. Claims 61-80 drawn to a method of producing antibodies , classified in class 435, subclass 326.

Applicant elected Group 1 claims 1-40.

The Examiner also imposed a species election in the prior action and required the Applicant to elect one species of the T helper cell epitope, one species of the $A\beta_{1-42}$ peptide and one species of the claimed immunogen. Applicant elected SEQ ID NO:51, SEQ ID NO:67 and SEQ ID NO; 73 respectively with traverse.

Now, the Examiner insist that the examination will only be directed to the species elected for the T helper cell epitope, SEQ ID NO: 51 and has refused to examine all of the other species in claims 1-41. Applicant had pointed to Table 2 to show the relatedness of the T helper cell epitopes and 3 and of the $A\beta_{1-42}$ peptides. However, the content of Tables 2 and to Table 3 to show the relatedness of the $A\beta_{1-42}$ peptides. However, this was entirely ignored by the Examiner.

Applicant also wish to point out that under the rules for election of species requirement, the Examiner is required to proceed to search and examine all of the species within claims 1-40 and cannot arbitrarily decide to exclude all of the other species from the present examination. In particular, as pointed out in the restriction requirement, claims 3, 11, 13, 23, 31, and 33 are claims within Group 1 and should not be excluded from the present examination since they are within the elected Group.

The change in the position of the Examiner by making the election of species into a restriction requirement is improper and should be withdrawn.

Claim Objections

The Examiner objected to claims 1-2, 4-9, 12, 14-22m 24-29, 32 and 34-40 as reciting improper Markush groups.

A Markush group refers to a grouping of molecules that share the similar structure or function. Claims 1 and 12 are the generic claims. Claim 1, part i) recite T helper cell epitopes selected from the group SEQ ID NO 1-64. These sequences represent linear peptides which are T helper epitopes. Therefore, they share a similar structure and function. Moreover, many of these T-cell epitopes are modified from either the MVF or the HBV surface antigen. Table 2 presents the structure of these epitopes in three groups, SEQ ID NO:1-22, known promiscuous T helper cell epitopes; SEQ ID NO:22-51, MVF T cell epitope and modifications thereof ;and SEQ ID NO:52-64, HBV surface antigen T cell epitope and modifications thereof, which are clearly related in structure. These peptides serve to present the $A\beta_{1-42}$ peptide to the B-cells. The Examiner has not stated clearly why this grouping is improper.

Claims 1 part ii recite a 10-28 amino acid sequence from the N-terminal of the $A\beta_{1-42}$ peptide. Clearly, these 10-28 amino acids of the $A\beta_{1-42}$ peptide share a common 10 amino acids structure. Thus, the objection for improper Markush grouping is clearly in error and should be withdrawn.

As for Claim 12, the structure of the peptide immunogen is presented as having two alternate structures, where the T helper epitope can be placed at the N terminal of the carboxy terminal of the $A\beta_{1-42}$ peptide fragment.

$(A)_n$-(N-terminal fragment of $A\beta_{1-42}$ peptide)-$(B)_o$-$(Th)_m$-X;

or

$(A)_n$-$(Th)_m$-$(B)_o$-(N-terminal fragment of $A\beta_{1-42}$ peptide)-X;

Then the parts of the structure, A, Th, B and X are individually defined as Markush groups. The rejection for improper Markush grouping for these is clearly in error and should be withdrawn.

The Examiner seems to think that the above claims recite a non-contiguous sequence. As presented, the claims are directed to contiguous sequences comprising a combination of sequences. This does not mean that the claimed sequences are not contiguous. There is no rule against such types of claims as demonstrated by the patents that has issued to United Biomedical, Inc., the assignee.

Rejection under 35 U.S.C. §101

The Examiner rejected claims 1-2, 4-8, 12, 14-22, 24-28, 32, and 34-40 as being directed to non-statutory subject matter. The Examiner stated that the "peptide immunogens claimed do not necessarily reflect the hand of man and potentially read on a product of nature."

The Examiner has not provided any evidence to support for this conjecture. Under the law, the burden is on the Examiner to show that the claimed invention is a 'product of nature' existing as claimed. As far as Applicant is concerned, no such materials exist in nature. Since there is nothing in record to support this rejection, it is improper and should be withdrawn.

Rejection under 35 USC §112

The examiner further rejected claims 1-2, 4-8, 12, 14-22, 24-28, 32, and 34-40 for containing matter that is not described in the specification in such a way as to convey to those of ordinary skill in the art that the inventor had possession of the claimed invention.

Apparently, the Examiner objects to a written description that embraces multiple embodiments, varying combinations of: independent amino acids, N-terminal fragments of beta amyloid peptide, linking groups and T helper cell epitopes. It is apparent that the Examiner clearly understood that the claims are directed to a combination of five different possible elements, with a minimum of two: N-terminal fragments of beta amyloid peptide, and T helper cell epitopes.

The specification provided 64 T helper epitopes, stated what the independent amino acids may be, five linking groups and the 10-28 N terminal amino acids of the beta amyloid peptide. Examples of how the elements of the claims are linked are

presented in the application. It is apparent that the rejection is merely based on the fact that this is a combination claim and can have a multitude of embodiments. This is not the basis of a rejection for lack of written description.

The Examiner pointed out that the immunological function is related to the structure of the peptide. This is true.

However, Applicant would like to point out that the claims provided sequences showing the structure of the claimed peptide immunogen. It is well known that there can be modifications in the sequence without affecting the overall structure of the peptide. These modifications without structural change are the so called functional analogs, which in the present case are immunologically functional analogs. The analogs may contain conservative substitutions. For example, an amino acid may be substituted with another that is of the same polarity, or same size and will still retain its structure and the biological function based on that structure. There may be mutations from one individual to another to form alleles. However, these mutations from one individual to another will not change the overall structure of the protein and as a consequence, the protein will still retain its biological function. This information is published in college level Biochemistry texts. For example, White, Handler and Smith, Chapter 5 of Principles of Biochemistry groups amino acids into neutral amino acids which may be aromatic, sulfur containing, or dicarboxylic acids; basic amino acids and other amino acids. The substitution of an alanine with glycine or valine will not alter its biological function. This is well known to those of skill in the art.

The specification clearly informs those of skill in the art that it is the 10 to 28 N terminal amino acids of the beta amyloid peptide. There may be variations in the sequence based on the variations in the protein as it occurs naturally in each person. These are the immunologically functional analogs. In addition, conservative substitution can also create analogs that functions as a B cell epitope for immune binding to an antibody or to provoke the production of antibodies that would bind thereto.

This description is clear to those of ordinary skill in the art to which the invention pertains and clearly shows that the inventor is in possession of the claimed invention, including the immunologically functional analogs of the 10 to 28 N terminal amino acids of the beta amyloid peptide. It is eminently proper for the inventor to

claim all the possible variations of the claimed invention as long as it is clearly described such that the person of ordinary skill in the art knows that the Applicant is in possession of the invention and there is sufficient description to enable those of skill in art to practice the invention.

The Examiner poses the situation wherein directed mutagenesis which proteins that differ in native conformation, immunological recognition, binding and toxicity. It is clear to a person of ordinary skill in the art that these are not immunologically functional analogs and are excluded from the claimed invention.

The specification not only described and provided 30 species of the MVF T-helper cell epitope alone. It also provided the way in which the T helper cell epitope may be varied by the use of the information provided in WO 99/66957, and listed in Tables 1 and 2.

Thus, the rejection of the claims on grounds of lack of written description of immunologically functioning analogs should be withdrawn.

The Examiner further contends that there is no data showing that there is a reduced level of beta-amyloid plaques within the brains of Alzheimer patients.

Applicant wish to point out that on page 5, paragraph 13 of the specification, published references have shown that data showing that antibodies that bind to the beta amyloid protein plaques have been shown to be effective to induce the clearance of pre-existing amyloid plaques. See Bard et al., Nature Medicine, 2000; 6:916-919. Applicant has shown that the claimed immunogen peptides are useful in generating antibodies that bind to amyloid protein plaques in the brain and the blood vessels of humans. See Examples 5, 6, and 7 and the results presented in Tables 5, 6, 7, 8, 9 and 10 and the drawings Figs. 1a to 1f and 2a to 2e. The electron-micrographs show that the antibodies raised against the claimed immunogen bound to senile plaques and amyloid plaques in human brains. Whereas, there is no binding when pre-immune sera is used. Thus, there is ample data to support utility. for showing the effectiveness of the antibodies generated.

The Examiner further rejected claims 1-2, 4-8, 12, 14-22, 24-28, 32 and 34-40 under 35 U.S.C. §112, second paragraph for being unclear and indefinite. The arguments presented above applies with equal force to the basis for this rejection.

The specification clearly sets forth 28 analogs for one of the T helper cell epitopes, which are immune enhancing analogs, since the T helper cell epitopes enhances the immunological function of the B cell epitope. The point raised by the Examiner is a conjecture without proper support from any publication. Reconsideration is requested.

Rejection under 35 USC §102.

Claims 12 and 15 are rejected as anticipated by US Patent 5,753,624. Although a copy of the cited reference was not enclosed, Applicant has obtained a copy to avoid further delays in the examination of this application.

A review of McMichael et al, '624 patent, claim 1 and column 7 shows that the patent teaches the use amyloid protein or the first 28 amino acids as an immunogen. The amyloid protein was combined with thimerosol in a pharmaceutically acceptable carrier. Thimerosol is an adjuvant compound. There is no teaching or suggestion of the use of a T helper cell epitope by McMichael et al.

Under the law, to find anticipation, each and every element of the claimed invention must be disclosed in the cited reference. McMichael et al. does not teach anywhere in the patent that the amyloid protein or the first 28 amino acid is covalently linked to a T-helper cell epitope selected from SEQ ID NO: 1-64 or an immune enhancing analog thereof. In fact, no where does McMichael teach an immune enhancing analog of SEQ ID NO: 1-64.

Thus, the rejection on this ground is improper under the law and should be withdrawn.

The Examiner also cited Kumar et al. as a reference. A copy of this reference was not provided with the Office Action. Therefore, a proper response cannot be made. However, the Examiner made similar statements except that it is stated that Kumar et al. teach antibody produced via immunization with a synthetic peptide of the first 14 amino acids of beta amyloid. Assuming this to be true, Kumar et al. does not teach the use of a T cell epitope covalently linked to the 14 amino acids. There is no teaching of the use of SEQ ID NO: 1-64 or an immune enhancing analog of SEQ ID NO: 1-64. Since this is absent in Kumar et al., anticipation cannot be found and the rejection should be withdrawn.

Applicant would appreciate receiving a copy of each of the cited references cited in the Notice of References Cited issued by the Examiner as is required by the rules.

Rejection Under 35 U.S.C. 103

Claims 1-2, 4-8, 12, 14-22, 24-28, 32, and 34-40 were further rejected for being obvious in view of five references:

Wang et al. WO99/66597;

Wang et al. WO 99/66952,

Behrouz et al. J . of Gerontology

McMichael et al. and

Kumar et al. cited above.

Applicant submitted WO 99/66597 and WO 99/66592 as prior art. However, a copy of Behrouz et al., McMichael et al. and Kumar et al. were not provided with the Office Action as required, making it very difficult to respond to the rejection on this ground.

However, Applicant request reconsideration based on the data submitted in the application. On page 41 Table 6, data was presented using SEQ ID NO: 67, the first 14 amino acids of the beta amyloid protein and SEQ ID NO: 66, the first 28 amino acids of the beta amyloid protein. the data shows the titer of the antibodies produced. as being about 1.0 and 3.5 respectively after 6 weeks. On the same table, data for SEQ ID NO: 70 is for the immunogen wherein SEQ ID NO: 66 was conjugated to a T helper epitope, SEQ ID NO:1, the titer increased to 4.3, almost 10 fold increase. When the T helper cell epitope is from the MVF, the titer of the antibodies specific to the beta amyloid peptide is even higher, an increase of about 2 log units or 20X. This is surprising and unexpected.

It is true that WO 99/66592 teaches the use of artificial T helper cell epitopes to enhance the immunogenicity of LHRH and the reference did suggest that the T helper cell epitope may be helpful in enhancing the immunogenicity of peptide immunogens such as somatostatin, a CD4-CDR2 peptide from HIV, IgE, FMDV, Cholesteryl ester transport protein (CETP). However, no data was provided with the

suggestion. There is no suggestion that the T-helper cell epitopes would be useful with the beta amyloid protein fragments and that the antibodies would bind to the beta amyloid plaques.

Moreover, the predictability of effectiveness in the vaccine technology is low. Therefore, at the most, it may be obvious to try and use T helper cell epitopes with the beta amyloid protein fragments. However, the level of specific antibodies produced cannot be predicted. In the present case, the dramatic increases in the levels of specific antibodies produced are surprising and unexpected. Based on the surprising and unexpectedly high level of antibodies produced by the use of the claimed invention, the rejection for obviousness should be also be reconsidered and withdrawn.

The Examiner had indicated that claims 10 and 30 are allowable. Applicant request that the examination be continued for the other species of the invention that are within the group that was elected.

The present response with a request for reconsideration is being filed pursuant to the suggestion of Dr. Gary Kunz, the Supervisory Examiner after a discussion on the treatment of the restriction requirement and the species election requirement. It is believed that a face to face interview of the issues raised may help to resolve some of the issues raised by the Examiner.

Respectfully Submitted,

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Date: October 1, 2003

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